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ASTHMA AND HAY FEVER

Air-Flow Obstruction in Allergic Asthma and Its Effect on the Lung Compartments. Syner, J. C.: U. S. Armed Forces M. J. 9: 1462, 1958.

The role of air-flow obstruction as a precursor and aggravator of obstructive pulmonary emphysema, a concept not universally accepted, was studied. The basic approach involved relating the duration of air-flow obstruction to the severity of alterations in lung compartment relationships, with particular focus on the size of the functional residual capacity (FRC) and the ratio of residual volume to total lung capacity (RV/TC). The 42 asthmatic cases in this study fulfilled about 80 per cent of the usually accepted criteria necessary for a diagnosis of allergic bronchial asthma. All the studies were performed at a time when the patients were free of attacks. Conventional pulmonary function studies included gross spirometry, calculation of specific flow rates, and measurement of lung compartment volumes and relationships. Since the functional residual capacity (FRC) and the ratio of residual air to total lung volume (RV/TC × 100) were regarded as important diagnostic and quantitative expressions of pulmonary emphysema, they were selected as the principal measurements for quantitating the presence and degree of severity of the emphysematous state. Data on the per cent of predicted normal FRC and the RV/TC × 100 in 30 normal persons, used as a control group, demonstrated that 130 per cent of the predicted normal was the approximate upper limit of normal in any age group. A rise in the ratio of residual volume to total lung volume was noted with increasing age, but it was found that a ratio of greater than 35 per cent generally indicated the presence of a significant degree of emphysema. The studies suggested that perennial asthma was more traumatic on this lung compartment than the seasonal type. Of 14 patients with seasonal asthma, 7 were within the normal range, and of 28 patients with perennial asthma, only 3 were normal. In comparing the RV/TC ratios of normal and asthmatic patients, it was found that whereas 95 per cent of the nonasthmatic persons fell within normal limits, 72 per cent of the asthmatic patients had abnormal ratios. The FRC in patients with seasonal asthma was less affected by the duration of symptoms than in patients with perennial asthma. Eighty-nine per cent of patients with perennial asthma, symptomatic in excess of 11 years, developed an elevation of FRC greater than 170 per cent of predicted normal. Symptoms beyond 10 years in duration resulted in the development of a more severe degree of abnormality in the size of this lung compartment. The RV/TC ratio was so variable that it was not dependent upon the duration of symptoms for the degree of abnormality encountered. This was consistent with the fact that the RV/TC ratio, unlike the FRC, was dependent upon the expiratory capacity which may be highly variable, depending upon the nature of the patient's effort and the degree of air-flow obstruction. It was concluded that the time for the control of air-flow impairment and prevention of irreversible large lung volume disease was within the first 10 to 15 years following the onset of asthma. Symptoms in excess of 10 years resulted in an elevation of the FRC that was greater than 190 per cent of predicted normal in the vast majority of cases studied. It was concluded that even during the so-called asymptomatic period, significant air-flow obstruction and resultant air trapping and hyperinflation of the lung volume existed in asthmatic patients. This implied the need for continuous medical management. The absence of wheezes and rhonchi in these patients must not be accepted as evidence that air-flow obstruction is not present. E. W.

Allergy Related to Bronchiectasis in Children. Lipschutz, A.: Ann. Allergy **17**: 336, 1959.

Bronchiectasis is not an uncommon complication of allergic respiratory disease in children. Bronchial dilation due to allergy can take place as the result of recurring allergic bronchitis, bronchial asthma, or by the traction placed upon the bronchial walls from without as may occur following pneumonia. Routine roentgenograms do not always reveal the pathology; bronchograms are necessary for accurate diagnosis of bronchopulmonary disease in infants and children. Bronchiectasis must be differentiated from congenital cystic disease of the lung and other developmental defects. Many allergic children with histories of recurrent coughs and colds have "hidden bronchiectasis" which becomes activated only in adult life after bronchial irritation. Bronchiectasis is usually associated with chronic cough, expectoration, and frequent respiratory infections, but these symptoms may be minimal or masked by the injudicious administration of antibiotics.

Three cases of bronchiectasis occurring in allergic children, each of whom had positive skin tests, are presented. H. F.

The Study of Allergic Reactions in the Etiology of Bronchiectasis. Goldman, S. L.: Ann. Allergy **17**: 399, 1959.

Allergic respiratory disease is not infrequently associated with bronchiectasis. The thick mucous secretions which plug the bronchi of the asthmatic patient may be the direct cause of the bronchiectasis. These plugs produce atelectasis and secondary infections which cause degeneration and rupture of the elastic fibers of the bronchial wall.

When allergy and bronchiectasis coexist, the bronchiectatic process may in some cases be reversed by proper allergic management. Such therapy should be instituted whenever indicated before resorting to surgical intervention.

Several case reports are presented to illustrate the relationship between the two conditions. H. F.

Triamcinolone Therapy in Chronic Bronchial Asthma. Levin, L., and Schwartz, E.: New York J. Med. **59**: 2710, 1959.

The authors studied the effects of triamcinolone therapy on 50 patients with chronic intractible asthma. The dosage ranged from 1 to 16 mg. daily, with the initial dose averaging 6 to 8 mg. and the average maintenance dose ranging from 2 to 4 mg. All other steroids were discontinued before the institution of triamcinolone therapy, but all other routine measures used for symptomatic relief were continued. Twenty-six of the 50 asthmatic patients reported excellent results after the new steroid was added to their treatment program, 20 patients experienced good results, and 4 patients obtained only fair improvement. None of the patients had to stop therapy because of side effects, which consisted of moon facies, weight loss, tachycardia, increased urination, and weakness and occurred in 16 per cent of the cases. Adequate dosage was an important consideration. R. W.

DERMATOLOGY

Development of Multiple Sensitivities From Primary Sensitivity to Nickel. Gaul, L. E.: Ann. Allergy **17**: 209, 1959.

Among 234 patients with contact dermatitis who were patch tested with a series of organic and inorganic materials, 16 were found to be sensitive to

nickel. Of these, 7 patients gave positive reactions only to nickel. In these cases the original site of the dermatitis was small, seldom measuring over 1 cm. in diameter, and the patch reactions were slight. Four of the 7 patients had no prior history of dermatitis, while the remaining ones had had mild dermatitis.

Combined sensitivity to both inorganic and organic substances, such as benzocaine, formalin, and perfume, was found in the remaining 9 patients. In these cases the original dermatitis bore no relationship to the presenting dermatitis which was always widespread and characterized by vesiculation and weeping. Three of these patients suffered long periods of disability. Four had developed chronic dermatitis characterized by flexural eczema and were adversely affected by environmental stress. The development of multiple sensitivity in patients primarily sensitive to nickel demonstrates that the initial lesions can easily become worse through contact with other materials, notably cosmetics and medications. When this happens, a further broadening of the allergic base takes place through cross-sensitization.

The author states that the diagnosis and treatment of primary nickel sensitivity are relatively simple when compared to the difficulty encountered in the diagnosis and management of multiple contact sensitivity.

Contact dermatitis is regarded as a nonstatic condition which is easily influenced by exposure of the skin to environmental or therapeutic allergens. When the skin is free of lesions, however, no increase in susceptibility to the common irritants is present and there appears to be a remarkable and unswerving specificity of the sensitivity reactions. H. F.

Problems of Contact Dermatitis in the Atopic Individual With Reference to Neomycin and Ragweed Oil Sensitivity. Jillson, O. F., Curwen, W. L., and Alexander, B. R.: Ann. Allergy **17**: 215, 1959.

Although contact dermatitis in the nonatopic patient is usually a simple diagnostic and therapeutic problem, the presence of atopy may produce aberrations in the clinical picture. It is therefore important to rule out the presence of atopy in any patient suffering from a contact type of sensitivity. In addition to the generally accepted criteria for labeling a patient as atopic—namely, a positive family and personal history for hay fever, asthma, or eczema and the presence of whealing reactions to direct and indirect skin tests—the authors employed other standards. These consisted of the presence of the extra eyefold referred to as Dennie's line, the cold pressor test, the blanching phenomenon to acetylcholine or to Trafuril ointment, and the histopathology produced in the skin of atopic patients after patch testing with such substances as chrome, nickel, neomycin, and ragweed oil. This finding is described as a localized, well-circumscribed, intraepidermal vesiculation or spongiosis which is characteristically periporal in location. While none of these factors singly is diagnostic of atopy, collectively they are of great help in evaluating the status of the patient.

Neomycin and ragweed-oil sensitivities are frequent complicating factors in contact dermatitis occurring in atopic persons, and produce the histopathologic picture described above. These findings are at variance with earlier observations which suggested that sensitivity to ragweed oil rarely occurs in ragweed-pollen-sensitive patients. The authors report 6 cases of ragweed-oil contact dermatitis in persons classified by them as atopic. Two of the 6 gave immediate wheal reactions to an intracutaneous test with ragweed pollen extract; another had a history of rhinitis during the ragweed season but failed to show a positive skin reaction. The remaining 3 patients were classified as being atopic on the basis of the criteria noted above. H. F.

OTORHINOLOGY AND OPHTHALMOLOGY

The Influence of Some Expectorants on the Rate of Ciliary Beat in the Trachea of Living Rats. Dalhamn, T.: A. M. A. Arch. Otolaryng. **68**: 20, 1958.

The rate of ciliary beat of the trachea of living rats was recorded. Then 0.5 c.c. of one of a number of expectorant drugs was introduced into the rats' stomachs by a tube. Immediately thereafter and 15 minutes later recordings of the rate of ciliary beat were again made. Sodium citrate, potassium iodide, sodium lauryl sulfate, polyoxyethylene sorbitan monolaurate (Tween 20), and polyoxyethylene sorbitan mono-oleate (Tween 80) brought about significant and rapid increases in the rate of the ciliary beat. On the other hand, ammonium chloride and extracts of ipecac and senega failed to cause a definite acceleration of the ciliary beat. In view of the fact that the ciliary activity is not the only important factor in the mechanism of expectoration, it is suggested that those expectorants which failed to accelerate ciliary activity may nevertheless be useful. B. S.

Transfer of Experimental Panophthalmitis in Rats by Parabiosis. Pfeiffer, E. F., Schoffling, K., Treser, G., Bachrach, I., Menk, W., Kurus, E., Otto., J., and Sandritter, W.: Proc. Soc. Exper. Biol. & Med. **100**: 467, 1959.

The injection of rabbit-anti-rat-eye antibodies into rats produced experimental panophthalmitis in 36 of 40 animals within 24 hours. Because whole eyes had been used for rabbit immunization, the pathologic process in the rats involved all parts of the eye but no other tissues. From 8 to 43 days after the serum injection, normal rats were joined in parabiosis to animals with eye lesions and kept under observation for from 5 to 49 days. In 21 out of 25 pairs, the ophthalmitis developed in the previously normal animal within 4 to 12 days postoperatively, and within 11 to 50 days after the serum injection in the primary ophthalmitic rat. The transferred ophthalmitis was similar in every way to that observed in the primary series. It has not yet been established whether the panophthalmitis in the parabionts was caused by the transfer of surviving antibodies or to "some other not yet clearly determined secondary tissue damaging factor." B. S.

MISCELLANEOUS ALLERGIES

Cold Sensitivity Syndrome. Goldberg, E. E., and Pittman, D. R.: Ann. Int. Med. **50**: 505, 1959.

Cold hypersensitivity, although rarely described in the literature, is not an uncommon clinical entity. Patients suffering from this condition usually fall into one of three groups: (1) those with a familial tendency to the condition, (2) those in whom the condition is associated with other diseases (notably syphilis and essential cryoglobulinemia), and (3) those experiencing sporadic attacks unrelated to a familial tendency or associated diseases. No clearly defined etiology has been found. The condition may be based on an exaggerated response of the peripheral vascular tree to cold with release of an H-like substance. It has also been postulated that the condition may be due to a defect in the heat-regulating mechanism in the body or to an allergic reaction. The latter theory has been substantiated by the demonstration of transferable cold reagins by means of the Prausnitz-Küstner technique.

Good clinical response has been obtained in certain cases with antihistamine therapy or with histamine desensitization. Steroids have been used to

block the reaction to cold and in some cases have brought about the disappearance of cryoproteinuria.

A case of cold sensitivity in a patient with a negative family history, but with symptoms of the type generally seen in familial cases, is presented.

H. F.

Hypersensitivity to Phenylcarbinol Preservative in Vitamin B_{12} for Injection. Lagerholm, B., Lodin, A., and Gentele, H.: Acta allergol. **12**: 295, 1958.

A 28-year-old man with psoriatic arthritis was given a series of vitamin B_{12} injections. The medication contained 15 mg. phenylcarbinol (benzyl alcohol) per milliliter as a preservative. After an initial favorable response, the symptoms recurred and were accompanied by urticaria and itching. It was observed that the platelet count fell from normal to 45,000 in 60 minutes following the B_{12} injection. When a B_{12} preparation without preservative was given, no fall in platelet count or untoward reaction occurred. This was cited as evidence that phenylcarbinol was the causative agent in this unusual reaction.

M. C.

ANAPHYLAXIS

Acute and Protracted Anaphylactic Shock in Guinea Pigs After Subcutaneous Injection of Antigen. Stone, S. H.: J. Immunol. **82**: 138, 1959.

Anaphylactic shock was induced in guinea pigs by the subcutaneous injection of antigen into actively and passively sensitized animals. Sheep and rat red blood cells and egg albumin, mixed with saline or with incomplete adjuvant, were used to stimulate antibody production.

Guinea pigs actively immunized with antigen-adjuvant combination responded to subcutaneous challenge with the homologous antigen by exhibiting a protracted shock syndrome consisting of pruritus, dyspnea, erection of the skin papillae, fall in body temperature, and eventual death; this syndrome evolved over a period of from one to thirty hours. Postmortem examination revealed mural hemorrhages and/or vascular stasis in the upper gastrointestinal tract. The lungs were grossly normal. Animals sensitized with an antigen-saline mixture and similarly challenged suffered a more acute shock with gross pathologic findings particularly pronounced in the lungs which were markedly emphysematous.

In animals which had been passively sensitized with rabbit or guinea pig immune serum, there was a direct relationship between the amount of sensitizing antibody and the time interval between subcutaneous challenge and death. Guinea pigs which had been passively sensitized 19 to 20 hours prior to challenge suffered protracted rather than acute shock if they were given an intravenous dose of homologous antibody immediately prior to receiving the challenge dose of antigen. Subcutaneous challenge of animals passively sensitized immediately prior to the eliciting injection caused mild protracted symptoms. Acute shock reactions with marked pulmonary emphysema and death from asphyxia could be converted to the protracted type by injection of antihistamine drugs prior to subcutaneous challenge.

The authors are of the opinion that sensitized guinea pigs may suffer protracted rather than acute anaphylactic shock following subcutaneous challenge if an "excess" of antibody is present in the circulation of the animal. When small amounts of antibody are present in the circulation, there is little circulating antibody available to hinder antigen-antibody union at the cellular level (the cells of the bronchiolar musculature) and acute anaphylactic death from asphyxia results.

D. Stein.

Passive Cutaneous Anaphylaxis With Antigen-Antibody Complexes and Additional Antigen. Rosenberg, L. T., Chandler, M. H., and Fischel, E. E.: Proc. Soc. Exper. Biol. & Med. **98**: 451, 1958.

Mixtures of antigen and antibody, varying from great antigen excess to antibody excess, and solutions of washed specific precipitate were tested for their ability to react *in vivo* to subsequent introduction of antigen. Anti-egg-albumin antisera were prepared by injecting guinea pigs with 4 times recrystallized egg albumin. Antigen-antibody combinations were prepared by adding varying amounts of antigen to appropriate dilutions of the guinea pig antisera. The presence of antigen excess was confirmed by capillary precipitin test. Specific precipitates were made by adding excess egg albumin to a pool of guinea pig antisera. These were washed 3 times in saline, and the presence of antigen excess was confirmed by testing the first supernate. Antibody nitrogen (AbN) determinations were carried out by the Markham modification of the micro-Kjeldahl procedure.

Male albino guinea pigs were injected intracutaneously in the flank with 0.1 ml. of the material to be tested. An intravenous challenging dose of 1 mg. egg albumin and 0.5 ml. of a 5 per cent solution of T-1824 (Evans blue dye) to determine the specific reactivity of the skin sites to passive cutaneous anaphylaxis was administered either 2 or 18 hours after intracutaneous injection. The resulting reactions were generally more marked at 18 hours. Skin sites were observed for extravasation of dye 15 minutes after challenge. The area of dye leakage was measured after the animals were sacrificed and bled out and after the skin was reflected. Reactions were graded from 1- to 4-plus, according to the size and intensity of the blue spot. The skin sites of 2 guinea pigs sensitized with 0.2 mg. AbN showed positive passive cutaneous anaphylaxis reactions following the intravenous administration of 1 mg. egg albumin with blue dye. A positive reaction could also be elicited with as little as 0.02 μg. AbN present in the sensitizing precipitate. The injection of dye alone produced no dye localization at the site of injection of the precipitate. Reactions at skin sites containing 0.1 ml. of varying quantities and proportions of antibody mixed with antigen indicated that antigen-antibody complexes in the range of antigen excess are as capable of sensitizing guinea pig skin as are those with antibody excess or antibody alone. This occurred regularly with mixtures containing 0.15 μg AbN and, in a few instances, with solutions containing 0.03 and 0.01 μg AbN. Two sites injected with 0.15 μg AbN and excess antigen showed slight erythematous reactions after 18 hours and prior to challenge. These sites reacted positively to subsequent intravenous antigen administration. Comparable sites in control animals receiving dye alone or antibody and dye did not show dye localization. "Small amounts of antibody in the presence of excess antigen sensitize guinea pig skin so that challenge with intravenous antigen and dye elicits passive cutaneous anaphylaxis. The significance of the biological reactivity of antigen-antibody complexes is briefly discussed." H. S.

Biologic Reactivity of Antigen and Antibody in Specific Precipitate. Rosenberg, L. T., Chandler, M. H., and Fischel, E. E.: Proc. Soc. Exper. Biol. & Med. **100**: 649, 1959.

The authors sought to determine whether washed specific precipitates, injected intravenously, could sensitize guinea pigs to subsequent injection of antigen. Four times recrystallized hen egg albumin was employed as the antigen. Rabbit and guinea pig antisera were prepared, and antibody nitrogen determinations were made by quantitative precipitin studies. Precipitate was

prepared at equivalence or slight antigen excess. The precipitate was washed three times in cold saline and then, after vigorous shaking in chilled saline, was suspended in concentrations varying from 15 to 140 μg AbN/ml. Guinea pigs injected intravenously with precipitates prepared from rabbit antiserum were tested from 5 to 72 hours later with an intravenous dose of 1 mg. of egg albumin. Almost all of the animals that had received from 70 to 140 μg rabbit antibody N in specific precipitate showed symptoms of anaphylaxis when challenged 24 hours later, and 5 out of 19 died in acute anaphylactic shock. Animals receiving precipitates containing 15 to 30 μg AbN showed only mild evidences of sensitivity when challenged.

The authors also demonstrated that washed specific precipitate administered intravenously could act like an antigen in inducing passive local anaphylactic reactions at cutaneous sites in guinea pigs previously sensitized with antibody alone. Hence, the precipitates under the proper experimental conditions can act as either antigen or antibody. Some dissociation of antigen-antibody complex is assumed to occur in these experiments. There are also indications that "at equivalence the available combining sites on both antigen and antibody are not fully saturated." B. S.

Comparative Effects of Glycogen and Antigen-Antibody Reactions on Serotonin and Histamine in the Rabbit. Waalkes, T. P., and Coburn, H.: Proc. Soc. Exper. Biol. & Med. **101**: 122, 1959.

Horse-serum-sensitive rabbits were used to study the comparative effects of glycogen and of antigen-antibody reactions on the serotonin and histamine content of rabbit whole blood. Experiments were carried out in vivo and in vitro. The incubation of antigen-antibody complex precipitate or of glycogen with normal rabbit whole blood in vitro brought about a release of serotonin and of histamine from the platelets. Similar results were obtained when specific antigen was added to blood from sensitized rabbits.

The effects of intravenous injections of glycogen and of antigen-antibody complexes into nonsensitized animals were similar to those produced by the intravenous injection of the specific antigen into sensitized animals. In all cases serotonin and histamine were released from platelets so that content of these amines in whole blood was reduced while it increased in the plasma and in lung tissue. These results were accompanied by rapid loss of platelets and leucocytes from the circulating blood and trapping of platelets in the lungs. The importance of platelets and leucocytes during anaphylaxis in the rabbit is stressed. I. Chao.

PHARMACOLOGY, PHYSIOLOGY, AND PATHOLOGY

The Problem of Allergic Cutaneous Vasculitis. McCarthy, J. T., and Kesten, B. M.: Ann. Allergy **17**: 519, 1959.

A number of clinicopathologic entities which are probably based upon hypersensitivity and which involve principally the vascular system have been described under a variety of names. These vasculitides, which undoubtedly represent varying degrees of allergic vasculitis, may be separated into 3 groups, depending on the locus and severity of the vascular response, as follows: (1) predominantly dermal vasculitis, (2) hypersensitivity angiitis, and (3) necrotizing angiitis with granuloma. Included in the first group are nodular dermal allergide, allergic cutaneous vasculitis, dermatitis nodularis necrotica, and pyoderma gangrenosum. These conditions are quite similar and are characterized by mild to moderate systemic symptoms including headache

and joint pains along with recurrent skin lesions generally of a polymorphic nature, such as nodules, purpuric macules, and erythema multiforme lesions. Dermatitis nodularis necrotica, however, appears to be a more severe variety of this group. Pyoderma gangrenosum is an even rarer form, characterized chiefly by destructive ulcerations, and it occurs mainly in debilitated adults.

Hypersensitivity angiitis is a reaction to foreign sera or drugs which is characterized by a widespread, fulminating, fatal vasculitis involving all the organs of the body with the exception of the gastrointestinal tract and the pancreas.

The third group includes allergic granulomatosis, a condition which occurs in asthmatic patients and which is quite similar to periarteritis nodosa. Of diagnostic importance are nodules which tend to occur on the extensor surfaces of the arms and legs and on the scalp. These lesions are firm, usually nontender, a few millimeters to a centimeter in size, and vary from flesh color to purple in hue. Necrotic, hemorrhagic, and urticarial lesions may also occur. The histopathology of the skin lesions is characteristic of the general pathologic process which involves most of the organs of the body. Lethal midline granuloma, another member of this group, may be of either the local or the disseminate type. The local type is characterized by a chronic destructive granulomatous ulcerative involvement of the tissues of the upper respiratory tract. There is usually chronic rhinitis with some ulceration of the skin about the external nares. The sinuses and laryngeal mucosa may be similarly involved. Saddle nose deformity and obstruction of the upper respiratory tract ensue. Cachexia and malnutrition often result in death. The disseminate form presents evidence of a more generalized vasculitis without external ulceration of the perinasal skin. Lethal midline granuloma is believed to be identical to Wegener's granulomatosis, which is a rare condition difficult to distinguish from classical periarteritis nodosa. It presents the triad of pansinusitis, arteritis, and terminal renal insufficiency, and there is often a diffuse inflammatory process found in the lungs. The histologic picture is one of necrotizing vasculitis with granulomatous changes, involving the skin in most cases. Here again the cutaneous lesions consist of nodules which tend to group themselves on the extensor surfaces of the extremities, the volar aspects of the fingers, the scalp, and the trunk. Cogan's syndrome (granulomatous nonsyphilitic interstitial keratitis) and idiopneumonic granulomatosis have been considered clinical variants of Wegener's granulomatosis. Of all the above entities, only hypersensitivity angiitis and allergic granulomatosis associated with asthma appear to be of a specific allergic nature. Drugs, sera, and bacteria are the probable offending agents. However, in the remainder of the vasculitides described, although there is no definite evidence of specific hypersensitivity, there is considerable evidence pointing to the fact that sensitization to organic or inorganic substances in predisposed persons may serve to set off these peculiar clinical patterns. It has been suggested that all of these conditions may be similar in nature to the Sanarelli-Schwartzman phenomena.

A case of Wegener's granulomatosis and a case of chronic dermal vasculitis with respiratory and nasal symptoms are reported in detail. H. F.

Nodular Panniculitis After Massive Prednisone Therapy. Taranta, A., Mark, H., Haas, R. C., and Cooper, N. S.: Am. J. Med. **25**: 52, 1958.

Following the discontinuance of prednisone, 6 episodes of nodular panniculitis were observed in 3 rheumatic children who had been under treatment with this drug. All of the patients had received a long course of relatively high doses of prednisone. One to 13 days after therapy was stopped, sub-

cutaneous nodules appeared on the cheeks, arms, or trunk. These nodules were firm, pruritic, and tender; they ranged in diameter from 0.5 to 4.0 cm., and in some instances the overlying skin was red and warm. When prednisone administration was reinstituted, striking subjective and objective improvement was noticed. When the panniculitis was mild, the nodules disappeared spontaneously over a period of months, leaving an area of skin pigmentation. During some of the episodes, fever, joint pains, and heart failure occurred at approximately the time of appearance of the nodules.

Histologic study of the biopsy specimens from all 3 patients showed acute or subacute inflammation of the panniculus. The type of inflammatory cells changed with the age of the lesions. They were predominantly neutrophils and mononuclear cells in a 4-day-old nodule, while older nodules showed a greater number of histiocytes and giant cells. Some of the latter surrounded clefts, presumably negative images of fatty acid crystals dissolved out during processing of the section. Several histiocytes had foamy cytoplasm, suggestive of ingestion of fat released by destroyed adipose cells. The nodules observed in these patients differed from rheumatic nodules both clinically and histologically. The differential diagnosis of nodular panniculitis is discussed. It is suggested that nodular panniculitis should be added to the list of possible untoward reactions to steroid hormone therapy. E. W.

Wegener's Granulomatosis. Tuhy, J. E., Maurice, G. L., and Niles, N. R.: Am. J. Med. **25**: 638, 1958.

Wegener's granulomatosis is a rare fatal syndrome of unknown etiology, characterized pathologically by necrotizing granulomas of the respiratory system, focal necrotizing vasculitis, and focal glomerulonephritis, usually terminating in uremia. In the respiratory tract, the disease may produce severe sinusitis, destructive rhinitis, otitis, or ulcerative lesions of the oropharynx, larynx, and tracheobronchial tree. In addition, or as the sole respiratory manifestation, there may be one or more large inflammatory masses in the lungs, which sometimes cavitate. The vasculitis affects both arteries and veins and may result in widespread manifestations referable to the skin, joints, heart, spleen, parotid, or prostate glands, or elsewhere; these manifestations are often transitory or recurrent in nature. The signs of renal damage appear midway or late in the course of the disease, and death ensues after an average of six months from the onset of symptoms. The disease appears equally in both sexes in the fourth or fifth decades, in patients previously well and usually without allergic tendencies. Anemia, leukocytosis (occasionally with eosinophilia), and a rapid erythrocyte sedimentation rate are usually found. Antibiotic therapy has no apparent effect except on associated secondary infection. Treatment with steroids seems to ameliorate some of the symptoms without significantly affecting the renal lesions or the eventual fatal outcome.

Most authors agree that Wegener's granulomatosis should be considered a subgroup of polyarteritis nodosa with certain anatomic and clinical peculiarities. In Wegener's granulomatosis there is the peculiar, predominant, and aggressive character of the necrotizing lesions in the respiratory tract, and the renal involvement occurs with impressive regularity and severity. Tissue eosinophilia is not commonly found in Wegener's syndrome, and the clinical stigmas of allergies are usually absent. The authors agree with those who had previously reported 35 cases of this syndrome that Wegener's syndrome is a manifestation of hypersensitivity. E. W.

The Distribution, Excretion and Metabolism of C^{14} Labeled Tripelennamine (Pyribenzamine) by Guinea Pigs. Weinman, E. O., and Geissman, T. A.: J. Pharmacol. & Exper. Therap. **125**: 1, 1959.

Pyribenzamine (PBZ) labeled with radioactive carbon was administered intraperitoneally to guinea pigs. Their secretions, excretions, and tissues were then subjected to physical and chemical breakdown analysis to trace the pathways and degradation patterns of this drug. All tissues contained PBZ one hour after administration. Considerable amounts were present in the urine, bowel, and bile at this time. Over 90 per cent of the radioactivity was finally excreted in the urine; two-thirds of this consisted of conjugates which, when hydrolized, did not produce PBZ itself. Little antihistamine activity was left in the urinary excretory products. Liver slice digestion of PBZ produces a metabolite similar to that found as a conjugate in urine. "It seems likely that the major metabolic modification of tripelennamine consists of hydroxylation in one or more positions followed by conjugation, probably with glucuronic acid." E. K.

IMMUNOLOGY

The Duration of Responsiveness of Lymph Node Cells Transferred to Adult Homologous Recipients. Dixon, F. J., Weigle, W. O., and Deichmiller, M. P.: J. Immunol. **82**: 248, 1959.

The authors sought to determine how long donor lymphoid cells retained the capacity to react to antigenic stimulation administered after their transfer to x-irradiated homologous adult recipient animals. The question of antigenic competition among cells from donor animals which had been simultaneously and equally immunized with two noncross-reacting antigens was also investigated.

Donor adult albino rabbits were simultaneously and equally immunized with bovine serum albumin (BSA) and human gamma globulin (HGG), so that after approximately 6 weeks equal amounts of precipitin antibody to HGG and BSA were present in the sera. Nine weeks after the onset of immunization, cells from donor mesenteric and popliteal lymph nodes were transferred to recipient animals. The recipient rabbits had been subjected to total body irradiation prior to cell transfer.

The cellular antibody response to BSA administered intravenously to recipient rabbits at varying times after transfer was measured by the length of time isotopically labeled (I^{131}) antigen remained in circulation and by total serum anti-BSA titers. The antibody response was similar in groups of rabbits injected with antigen immediately after receiving donor cells or after intervals of one or six hours. When BSA was injected one day following cell transfer, its elimination from circulation was delayed and anti-BSA titers were detectable but low. If injection of BSA was delayed for 3 or more days after cell transfer, it remained in the serum as whole antigenic protein and no detectable anti-BSA titers were present.

Intravenous doses of HGG given at the time of cell transfer tested the ability of the transferred cells to make an antibody response. The fact that significant anti-HGG titers were produced indicated that the injected cells survived for at least 5 to 7 days after transfer. The antibody response to HGG had no effect on the total amount of BSA produced.

It is brought out that transferred cells cannot complete an antibody response when antigenic stimulation is withheld 3 or more days after cell transfer, because the transferred cells are rejected by a homograft reaction on the

part of the recipient which occurs at about the ninth day. X-rayed adult recipients react against homologous lymphoid cells as soon as, or sooner than, x-rayed neonatal recipients. D. STEIN.

Compatibility Factors Influencing the Acceptance of Rat Bone Marrow Graft by the Irradiated Mouse. Hollingsworth, J. W.: Yale J. Biol. & Med. **31**: 157, 1958.

Chromium-51-labeled rat erythrocytes injected into normal mice persisted in the circulation for about 3 days and then rapidly and completely disappeared. Mouse blood volumes, calculated from labeled rat erythrocytes 24 hours after injection, were approximately of expected theoretical values, indicating no sizeable immediate loss of rat erythrocytes from the circulation. The rapid disappearance of rat erythrocytes was associated with the appearance of anti-rat-erythrocyte agglutinins of variable titer in normal mice. When labeled rat erythrocytes were injected into irradiated isologous-marrow-treated mice, the life span of cells was not markedly decreased and no demonstrable anti-rat-erythrocyte agglutinins appeared in the serum. The disappearance rate of labeled rat erythrocytes in the irradiated mouse was similar to the curve of disappearance of chromium-51-tagged isologous and homologous mouse erythrocytes and autogenous rat erythrocytes. Chromium-tagged human, guinea pig, rabbit, and chipmunk erythrocytes were lysed almost immediately when injected into normal mice. Although some hamster erythrocytes persisted for several days, there was a large initial loss of cells. Irradiated mice did not accept foreign erythrocytes any better than normal mice, except that possibly there was some prolongation of hamster erythrocyte life span in irradiated mice. Correlation of these in vivo results with in vitro naturally occurring agglutinins or hemolysins was not successful. Antisera were produced in rabbits to a number of different rodent erythrocytes or rodent sera. These antisera were tested against a panel of appropriate rodent antigens. Rabbit antisera to rat and mouse erythrocytes revealed marked crossing of antigenicity. No cross reactivity was noted between rat or mouse antibodies and guinea pig or hamster anitgens. Hence, these studies confirmed and amplified the fact that the mouse and rat are immunologically very similar. E. W.

Some Surface Components to Haemophilus Pertussis: Immunizing Antigen, Histamine-Sensitizing Factor and Agglutinogen. Maitland, H. B., and Guerault, A.: J. Path. & Bact. **76**: 257, 1958.

This work confirms earlier reports that saline washing of *H. pertussis* will remove an antigen which is capable of protecting mice from challenge with the organism and that the washed bacteria still retain some of this protective antigen. Histamine sensitizing factor (HSF) was studied by the injection of test material (vaccine or washings) intraperitoneally into mice. Five days later a challenging dose of 6 or 30 mg. histamine was administered intraperitoneally. Normal mice were not killed by these doses, whereas sensitized mice died within 24 hours. The HSF material was found in bacterial suspension, washings, and washed bacteria, and all of these materials elicited anti-HSF antibody following injection into rabbits. Washings also contained agglutinogen. A mixture of thiourea, urea, and formamide (TUF) was more efficient than saline in removing antigenic components from the bacteria, and material so removed had a high mouse-protective value "which suggests that

such material might be a successful immunizing agent for children." Rabbit sera obtained after injection of vaccine suspension, washings, and TUF extract all contained transferable antibody protective to mice against intratracheal and intracerebral challenge. Human hyperimmune serum contained anti-HSF and agglutinin antibody and protected mice passively against intracerebral challenge. The washings of *H. pertussis* organisms gave chemical reactions "consistent with the presence in washings and extract of a protein-lipid-carbohydrate complex." E. K.

The Effect of 6-Mercaptopurine on Primary and Secondary Immune Responses. Schwartz, R., Eisner, A., and Dameshek, W.: J. Clin. Invest. **38**: 1394, 1959.

Rabbits were immunized with an intravenous injection of radioactive iodinated human serum albumin. Certain animals received a second antigen injection 6 to 12 weeks later. Experimental groups in each category were treated with 6-mercaptopurine in doses up to 6 mg. per kilogram per day for from 8 to 13 days. Blood serum was studied for the isotope content of its salt-precipitated globulin fraction, representing concentration of circulating antigen-antibody complexes; "free" antibody was measured by tannic acid hemagglutination. The primary immune response could be completely blocked by 6 mg. per kilogram per day of 6-mercaptopurine. With smaller doses, a linear relationship of antibody suppression and drug administration obtained. At a dose of 6 mg. per kilogram per day, antibody production under repeat antigenic stimulation was only partially blocked. It appears that 6-mercaptopurine acts as a nucleic acid antagonist and is probably synthesized into the nucleic acid molecules of certain cells. Several possible mechanisms are discussed to account for the inhibition of antibody formation. The drug-effect linearity suggests a first order chemical reaction rather than a direct cytotoxic effect as produced by radiation or nitrogen mustards. E. K.

MISCELLANEOUS

Antihistamines and Diphenylhydantoin-Induced Gingival Hyperplasia. Sturmer, F. C.: New England J. Med. **259**: 485, 1958.

It has been reported that a gingival hyperplasia secondary to the administration of diphenylhydantoin may be completely cleared in two or three months by the daily administration of sustained-release tablets of chlorprophenpyridamine maleate tablets. In this study the patients, who were all inmates of a state institution for mental defectives, had been receiving diphenylhydantoin for periods of 17 to 108 months for convulsive disorders. Their ages ranged from 4 to 32 years. The dosage of the anticonvulsant varied from 50 to 400 mg. daily. The degree of gingival hyperplasia was recorded as moderate in 6 patients, moderately severe in 9, and severe in 13. Sustained-release tablets were not employed in this study. Chlorprophenpyridamine maleate was given to 16 patients in doses of 4 mg. every 6 hours. Tripelennamine hydrochloride was administered in 5 patients in doses of 50 mg. every 6 hours, and diphenhydramine hydrochloride was administered to another 5 patients in doses of 25 mg. every 6 hours. Two patients received the latter drug in doses of 10 mg. every 6 hours. The results were evaluated by comparing color pictures that were taken of the gingivae before the start of drug treatment with those taken one day before the antihistamine drugs were discontinued 3 months later. It was concluded that antihistamines are without effect on diphenylhydantoin-induced gingival hyperplasia. E. W.

Antihistamine Therapy for Gingival Hyperplasia Due to Diphenylhydantoin. Holowach, J., Thurston, D. L., and Gilster, J. E.: New England J. Med. **259**: 180, 1958.

As a result of a report that antihistamine therapy reduced the regression of gingival hypertrophy induced by diphenylhydantoin, 4 children with gingival hyperplasia caused by this drug were given chlorprophenpyridamine maleate capsules in varying doses for 3 to 9 months. During the treatment period there was no significant reduction of the hyperplastic tissues; nor was there any increase in hyperplasia. E. W.

Studies on Allergenic Extracts. 1. A New Method for the Preparation of Mold Extracts Using a Synthetic Medium. Schaffer, N., Molomut, N., and Center, J. G.: Ann. Allergy **17**: 380, 1959.

A new synthetic medium for mold cultivation which appears to have certain advantages over other media is described. Contaminating allergenic materials as well as nonspecific irritants are eliminated by this medium.

Molds grown on such a medium were extracted by a method described in detail. This method of extraction at no time subjects the allergenic material to denaturing influences. The extracts prepared in this manner proved to be more specific, as determined by skin tests and confirmed by environmental studies, than extracts prepared from Czapek's medium and extracted in the usual fashion. H. F.

A Further Study of Kveim Reaction in Sarcoidosis and Tuberculosis. Israel, H. L., Sones, M., Beerman, H., and Pastras, T.: New England J. Med. **259**: 365, 1958.

The Kveim reaction, which is regarded as a reliable aid in the diagnosis of sarcoidosis, consists of the intracutaneous injection of a suspension made from the gland of a patient with sarcoidosis. The appearance of a persistent nodule at the site of injection within two months is considered to be a positive reaction. Recently, English and American investigators have insisted that the diagnosis must rest on the demonstration of epithelioid tubercles on histologic section of this nodule. In the present study, 60 patients with definitely proved sarcoidosis were subjected to the test. The test was successfully completed in 46 patients. No residua were detected in 10 patients, and biopsies were performed in 36. The histologic appearances of the nodules were classified as follows:

1. *Sarcoid reaction*—naked, sharply defined tubercles consisting of epithelioid cells, with or without giant cells or fibrinoid necrosis.
2. *Nonspecific granuloma*—diffuse epithelioid-cell formation, with or without giant cells or fibrinoid necrosis, differentiated from the sarcoid reaction by the absence of pattern or definition of tubercle formation.
3. *Chronic inflammation*—diffuse infiltration by mononuclear cells, fibroblasts, and newly formed vessels, with a scattering of lymphocytes and polymorphonuclear leukocytes.

Sarcoid granulomas indicative of a positive test were observed in 13 patients (28.3 per cent of those with complete tests), and nonspecific granulomas were present in 8 patients. Negative reactions and nonspecific inflammations were noted in 15 patients.

Forty patients with pulmonary tuberculosis were subjected to the Kveim test. The test was completed in 29. Biopsies were obtained in 22 patients exhibiting palpable or visible residua. None showed sarcoid granulomas; three (13.6 per cent) had nonspecific granuloma.

Twenty-five of the patients with sarcoidosis and 8 with pulmonary tuberculosis received simultaneous injections of test materials supplied by other investigators. The tests were completed in 25 cases. In 3, both tests were positive; in 15, both tests were negative. In 2 patients who showed negative reactions with the authors' material, the test materials obtained from other investigators gave positive reactions. In another patient with sarcoidosis, the authors' antigen yielded a sarcoid reaction, and the antigen obtained elsewhere gave a negative reaction. In three other patients with sarcoid, there was minor discordance of results. It was concluded that variability of the test material appeared to be the principal cause of inconsistent results, but variations in histologic interpretation also contributed to the difficulties encountered with this test. E. W.

Agranulocytosis Following Antihistamine Therapy. Report of a Fatal Case. Norris, B. F.: New York J. Med. **59**: 2606, 1959.

A 64-year-old woman was hospitalized because of abdominal pain, nausea, and diarrhea. She had developed a pruritic rash 4 months previously, for which parabromdylamine maleate (Dimetane) tablets and an ointment containing hydrocortisone and neomycin had been prescribed. She took 142 parabromdylamine tablets in divided daily doses during the following 7 weeks. A blood count done at the end of that time was reported as essentially normal. Her medication was changed to thenalidine tartrate tablets (Sandostene), 25 mg. 1 to 4 times a day, and continued until 56 days later when it was stopped at the time of her admission to the hospital. She gave a past history of migraine headaches. Examination on admission to the hospital revealed a temperature of 103.4° F., a small hemorrhagic reaction in the soft palate, and a total absence of granulocytes on the peripheral blood smear. The white blood count varied from 225 to 550 cells per cubic millimeter, and the bone marrow showed a total absence of granulocyte elements with a striking increase in plasma cells and a moderate number of lymphocytes. The patient was given large doses of ACTH, tetracycline, and penicillin but developed recurrent abscesses and expired on the eighth hospital day. Postmortem examination revealed scattered petechial-like lesions throughout the lungs and heavy infiltration of the adrenals with plasma cells and lymphocytes. A postmortem blood culture yielded a pure growth of *Escherichia coli.* Although there was an increased number of plasma cells, lymphocytes, and reticulum cells in the bone marrow, there was no evidence of myeloma disease on postmortem examination. In view of the patient's course, it was assumed that the agranulocytosis was caused by thenalidine. R. W.

Prognosis in Cases With Eosinophilic Pleural Effusion. 17 Cases Followed for Five to Twelve Years. Järvinen, K. A. J., and Kahanpää: Acta med. scandinav. **164**: 245, 1959.

Out of a group of 929 patients with exudative pleurisy, 17 were found to have eosinophil concentrations in their pleural exudates of from 10 per cent to 70 per cent. Most of the cases were observed in fall or winter, when there was no pollen in the air. The 17 patients ranged in age from 22 to 54 years, and 15 were males. In 10 cases there had been an antecedent respiratory in-

fection. One patient had a traumatic rib fracture 2 weeks prior to onset; 4 patients exhibited transitory pulmonary infiltrations; pulmonary infarction had been suspected in one three weeks before hospitalization. In 11 no other associated pulmonary disorder was discoverable. Duodenal peptic ulcer was present concomitantly with the effusion in 3 males and was suspected in a fourth. None of these patients gave a past history of atopy. Ten patients had a blood eosinophilia, which disappeared in 7 with the cessation of pleurisy. Eosinophilic pleural effusion cleared more rapidly than iodopathic exudative pleurisy. A follow-up study made 5 to 10 years later revealed that 2 patients had developed bronchial asthma, 2 others had pulmonary tuberculosis, and 2 had had a recurrence of pleurisy. In a control study of idiopathic exudative pleurisy, the tuberculosis morbidity was about 40 per cent. E. K.

ANNOUNCEMENT

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